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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

PIHONAK, SARAH

ART UNIT

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1627

MAIL DATE

DELIVERY MODE

12/09/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/577,385	Applicant(s) METTLER, HANSPETER	
	Examiner SARAH PIHONAK	Art Unit 1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 August 2009 and 19 November 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application, filed on 7/3/2006, is a national stage entry of PCT/EP04/11971, filed on 10/22/2004.

Priority

This application claims foreign priority to Application No. 03024865.2, filed on 10/31/2003.

Response to Remarks

1. Applicant's arguments filed 8/12/2009 and 11/19/2009 have been fully considered but they are not persuasive. Claims 1-23 were rejected as being unpatentable under 35 USC § 103(a) over Duprat de Paule et. al., US Patent No. 6,878,665, in view of Saito et. al., EP Patent Publication No. 1176135. The Applicant has argued that Duprat de Paule et. al. teaches away from the present invention, as Duprat de Paule et. al. teaches the catalytic hydrogenation of fluorinated unsaturated compounds with the ruthenium-Fluoxphos catalyst, but not the hydrogenation of chlorinated or brominated unsaturated compounds. Additionally, the Applicant has argued that the percent ee values of the selectively hydrogenated fluorinated compounds are considerably lower than the ee values obtained in the instant application. While these arguments have been fully considered, they are not found persuasive. While Duprat de Paule et. al. teaches the selective catalytic hydrogenation of fluorinated compounds with the ruthenium-Fluoxphos catalyst, the percent ee values of the resulting fluorinated alcohols approach 80%, depending on the reaction conditions. Additionally, Saito et. al. teaches that a high ee of 98.5% was obtained in

Art Unit: 1627

preparing the chlorinated alcohol compound, with the ruthenium-SEGPPOS catalyst.

The SEGPPOS ligand of the ruthenium-SEGPPOS catalyst is very similar to the Fluoxphos ligand, the difference being that the bis(methylenedioxy)biphenyl moiety of the SEGPPOS ligand is replaced with bis(difluoromethyldioxy)biphenyl to obtain the Fluoxphos ligand. As Saito et. al. teaches that selectively hydrogenated chlorinated alcohols can be prepared with high enantiomeric purity with the ruthenium-SEGPPOS ligand, one of ordinary skill in the art would have been motivated to perform this hydrogenation reaction of the chlorinated unsaturated compound with the ruthenium-Fluoxphos catalyst taught by Duprat de Paule et. al., because it is taught that the ruthenium-Fluoxphos catalyst is effective at preparing a wide variety of alcohol compounds of high purity. While Duprat de Paule et. al. does not explicitly teach that chlorinated or brominated unsaturated compounds can be selectively hydrogenated with the ruthenium-Fluoxphos catalyst, it is taught that a wide variety of unsaturated compounds can be selectively hydrogenated. Additionally, as Saito et. al. teaches that the chlorinated alcohols can be prepared with high percent ee with the structurally similar ruthenium-SEGPPOS catalyst, it would have been apparent to one of ordinary skill in the art that chlorinated alcohols can be successfully prepared with high percent ee; therefore, one of ordinary skill in the art would have been motivated to prepare the chlorinated alcohol with other ruthenium catalysts, such as ruthenium-Fluoxphos. The Applicant has argued that as Saito et. al. shows that chlorinated alcohols can be successfully prepared with the ruthenium-SEGPPOS catalyst, one of ordinary skill in the art would not have been motivated to prepare these alcohols with the ruthenium-

Art Unit: 1627

Fluoxphos catalyst, as Duprat de Paule et. al. shows lower ee values for the synthesis of fluorinated alcohols. However, the lower ee values apply to fluorinated compounds, and not to chlorinated or brominated compounds. As Saito et. al. teaches that chlorinated alcohols can be selectively prepared with high percent ee values with ruthenium catalysts such as the ruthenium-SEPHOS catalyst, one of ordinary skill in the art would have expected success in preparing chlorinated alcohol compounds with other ruthenium catalysts, such as the structurally similar ruthenium-Fluoxphos catalyst. Therefore, the rejection was proper and is maintained. Due to the claim amendments, a modified rejection of the claims is applied, which will be discussed below. New claim 24 has been added.

2. Claims 1-24 were examined.
3. Claims 1-24 are rejected.

Claim Rejections-35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

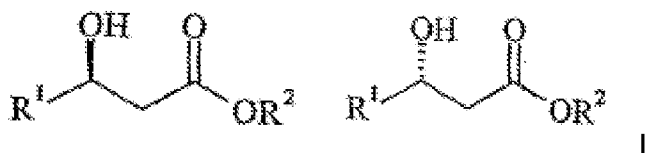
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

Art Unit: 1627

2. Ascertaining the differences between the prior art and the claims at issue.
 3. Resolving the level of ordinary skill in the pertinent art.
 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
6. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duprat de Paule et. al., US Patent No. 6,878,665, in view of Saito et. al., EP Patent Publication No. 1176135.
7. The claims are drawn to a process of preparing an enantiomerically pure (R) or (S) 4-halo-3-hydroxybutyrate of the formula I, with an enantiomeric excess (ee) between 93.2 to 98.1 %, or greater than 90%, for claim 24. The enantiomerically pure 4-halo-hydroxybutyrate compounds are prepared by selective hydrogenation of a compound of formula II with a ruthenium complex comprising the chiral Fluoxphos ligand. The compounds of formula I are shown below:



Where $R^1 = CH_2X$, CHX_2 , or CX_3 ; $X = Cl$ or Br ; $R^2 = C_{1-4}$ alkyl, C_{3-6} cycloalkyl, aryl, or aralkyl, each optionally substituted with one or more C_{1-4} alkyl groups or halogen atoms.

Duprat de Paule et. al. teaches a ruthenium catalyst for the asymmetric hydrogenation of keto-butyrate compounds, in which the catalyst comprises the Fluoxphos ligand (column 26, claim 11; column 25, claim 9; pp. 10-12, Table 1 reactants). Duprat de Paule et. al. teaches that the keto-butyrate compounds are selectively hydrogenated to form 3-hydroxybutyrate compounds (pp. 10-12, Table 1; column 26, claim 16). The enantiomeric excess of the synthesized alcohols is taught as

Art Unit: 1627

being greater than 99 %, for some 3-hydroxybutyrate compounds (pp. 10-12, Table 1).

It is taught that the ruthenium catalyst complex comprising the Fluoxphos ligand further comprises an alkene (p. 5, column 7, line 54), arene (p. 5, column 8, line 8), diene (p. 9, column 16, lines 60-65), and/or a polar solvent molecule (p. 5, column 7, line 55). It is also taught that the ruthenium-Fluoxphos complex comprises a ligand such as 1,5-cyclooctadiene (p. 9, column 16, lines 60-65) or p-cymene (p. 5, column 8, line 8).

Duprat de Paule et. al. also teaches that the catalytic hydrogenation is performed in solvents such as C₁₋₄ alcohols (p. 5, column 8, lines 59-60), dimethylformamide (p. 5, column 8, line 57), and further solvent additives, such as acid (p. 9, column 16, lines 60-65). It is also taught that the counterion of the ruthenium complex is Cl⁻, Br⁻, I⁻, BF₄⁻, ClO₄⁻, or PF₆⁻ (p. 5, column 8, lines 8-10). The preparation of the ruthenium complex by mixing [Ru₂Cl₄(benzene)₂] with the Fluoxphos ligand in a polar solvent such as tetrahydrofuran (p. 9, column 16, lines 10-17) is taught, and that the p-cymene ligand can be substituted for benzene (p. 5, column 8, line 8). The hydrogenation is performed with the hydrogen pressure range between 1 to 150 bar (p. 6, column 9, lines 16-17).

While Duprat de Paule et. al. teaches that the ruthenium-Fluoxphos catalyst is used successfully in preparing a wide variety of selectively hydrogenated alcohols with a high percent ee, such as greater than 99%, it is not explicitly taught that 4-chloro- or 4-bromo-3-hydroxybutyrates can be prepared with an ee value greater than 90%, or between 93.2 to 98.1 %.

Saito et. al. teaches that the ruthenium-SEGPHOS catalyst is effective in catalyzing asymmetric hydrogenations, such as the hydrogenation of ethyl 4-

Art Unit: 1627

chloroacetoacetate to ethyl (S)-4-chloro-3-hydroxybutanoate (pp. 9-10, example 6; p. 11, claim 1). Regarding the claimed compounds of formula I, ethyl (S)-4-chloro-3-hydroxybutanoate has the substituents defined as follows: $R^1 = CH_2Cl$; $X = Cl$; $R^2 = \text{ethyl}$. Particularly, it is taught that ethyl (S)-4-chloro-3-hydroxybutanoate is prepared with an ee of 98.5% (pp. 9-10, example 6). The SEGPHOS ligand taught by Saito et. al. and the Fluoxphos ligand taught by Duprat de Paule et. al. are structurally similar, in that both ligands share the same core structure. The difference between the two ligands is that for Fluoxphos, the bis(difluoromethyldioxy)biphenyl has replaced the bis(methylenedioxy)biphenyl moiety of the SEGPHOS ligand. Duprat et. al. teaches that the ruthenium-Fluoxphos catalyst is effective at preparing a variety of different alcohol compounds, with high enantiomeric selectivity for many. As Saito et. al. teaches that ethyl (S)-4-chloro-3-hydroxybutanoate is synthesized with high enantiomeric selectivity with the ruthenium-SEGPHOS ligand, one of ordinary skill in the art would have been motivated, at the time of the invention, to utilize other ruthenium catalysts, such as the structurally similar ruthenium-Fluoxphos catalyst, for the same reaction, because it is taught that ethyl 4-chloroacetoacetate can readily undergo asymmetric hydrogenation to form the alcohol product with high enantiomeric selectivity, and Duprat de Paule et. al. teaches that the ruthenium-Fluoxphos catalyst is effective at selectively hydrogenating a wide variety of compounds to form alcohols of high percent ee. Therefore, it would have been prima facie obvious to one of ordinary skill in the art, at the time of the invention, to utilize the ruthenium-Fluoxphos catalyst to prepare ethyl (S)-4-chloro-3-hydroxybutanoate with an ee of greater than 90%, because Saito et. al. teaches that the

Art Unit: 1627

alcohol can be readily prepared with an ee of 98.5 %, and Duprat de Paule et. al. teaches that the ruthenium-Fluoxphos catalyst selectively catalyzes the hydrogenation of a wide spectrum of compounds to form the alcohol products with high percent ee.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-every other Friday 8:00 AM - 5:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone

Art Unit: 1627

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627